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REVIEW

Targeting *KRAS*^{G12C}-Mutated Advanced Colorectal Cancer: Research and Clinical Developments

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Abstract: Identifying mutations in the *KRAS* gene has become increasingly important in the treatment of colorectal cancer with many prognostic and therapeutic implications. However, efforts to develop drugs that target *KRAS* mutations have not been successful until more recently with the introduction of the *KRAS*^{G12C} inhibitors, sotorasib (AMG510) and adagrasib (MRTX849). Both agents have demonstrated safety and promising efficacy in preclinical studies and early phase trials, but it appears that not all tumor types harboring the *KRAS*^{G12C} mutation are sensitive to monotherapy approaches. In particular, patients with colorectal cancer (CRC) derive less benefit compared to those with non-small cell lung cancer (NSCLC), likely due to rapid treatment-induced resistance through increased epidermal growth factor receptor (EGFR) signaling. As a result, combination therapy trials with EGFR inhibitors are currently underway. Here, we will review the available clinical trial data on KRAS^{G12C} inhibitors in *KRAS*^{G12C}-mutated CRC, possible mechanisms of resistance to monotherapy, the research studying why available agents are proving to be less efficacious in CRC compared to NSCLC, and future directions for these promising new drugs.

Keywords: *KRAS*^{G12C}, sotorasib, adagrasib, colorectal cancer, targeted therapy

Introduction

KRAS mutations are found in approximately 45% of colorectal cancer (CRC) and are associated with resistance to targeted therapies such as anti-epidermal growth factor receptor (EGFR) inhibitors.[1–3] The *KRAS*^{G12C} mutation is found in 14% of non-small cell lung cancer (NSCLC), 3% of CRC, and 1–3% of other solid tumors.[4–7] Patients with metastatic *KRAS*^{G12C}-mutant CRC progress quickly on standard of care chemotherapy regimens and may have shorter overall survival (OS) compared to those with non-*KRAS*^{G12C} mutations.[8]

The glycine-to-cysteine substitution at position 12 leads to a KRAS protein that is predominantly in the GTP-bound state, which drives constitutive activation of oncogenic signaling.[9–11] The mutant cysteine is located next to a pocket in the switch II region (S-IIP), which exists only in the inactive GDP-bound conformation of KRAS and has therefore been studied extensively to identify potential inhibitors of KRAS^{G12C}.[12,13] The existing inhibitors bind to the mutant cysteine, which disrupts the switch I/II region. This drives KRAS to favor the GDP- over the GTP- bound state and traps the protein in an inactivated state.[13,14] In addition, the occupation of the S-IIP region by these inhibitors disrupts downstream binding of effector proteins, such as RAF. In vitro studies found that these compounds lead to decreased viability and increased apoptosis in cancer cell lines harboring the *KRAS*^{G12C} mutation.[12,14] After overcoming several challenges in drug development, sotorasib and adagrasib (developed by Amgen and Mirati Therapeutics, respectively) are the two KRAS^{G12C} inhibitors with the most promising clinical activity in solid tumors.[15,16]

Targeting KRAS^{G12C} with sotorasib and adagrasib in mice bearing *KRAS*^{G12C}-mutant NSCLC tumors reduced the phosphorylation of ERK and led to significant tumor regression.[17,18] A Phase 1 clinical trial evaluating the safety and efficacy of sotorasib has demonstrated a tolerable safety profile as well as promising antitumor activity in patients with *KRAS*^{G12C} mutant solid tumors.[19–21] Based on the significant clinical activity in patients with NSCLC in the CodeBreak100 trial, sotorasib was approved by the FDA for patients with locally advanced or metastatic NSCLC

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harboring the *KRAS*^{G12C} mutation who had progressed on prior systemic therapy.[22] Similarly, based on data from a Phase 2 KRYSTAL-1 trial, adagrasib was approved in Europe for the same indications in NSCLC and is currently under review by the FDA.[23] Herein, this review focuses on the current development of direct KRAS^{G12C} inhibitors and alternative strategies for targeting KRAS, particularly in CRC where the effect of monotherapy appears to be limited.

Monotherapy with Sotorasib or Adagrasib in *KRAS*^{G12C}-Mutated Tumors

Sotorasib (AMG510)

In the first in human phase 1 study, sotorasib was evaluated with a dose-escalation design in patients with refractory *KRAS*^{G12C}-mutated solid tumors (NCT 03600883).[22] Doses were escalated from 160mg daily to 960mg daily. No dose limiting toxicities were noted in the escalation phase. The 960mg oral dose was selected for further development based on its safety and pharmacokinetics. Additional expansion cohorts of NSCLC, CRC, and other solid tumors with *KRAS*^{G12C} mutation were enrolled to include a total of 129 patients. Most patients enrolled in the study were NSCLC (59), followed by CRC (42) and other tumors (28). A total of 73 patients (56.6%) had treatment-related adverse events; only 15 (11.6%) patients experienced grade 3 or 4 events. Notable activity was noted in the NSCLC group with an objective response rate (ORR) of 32.2% and a disease control rate (DCR) of 88.1%. Median progression free survival (PFS) in this group was 6.3 months. Clinical activity was more modest in the CRC and other solid tumor groups. In the CRC cohort, the ORR was 7.1% and the DCR was 73.8%. The median PFS in this group was 4 months. Responses were also documented in the other solid tumors group, including patients with pancreatic, endometrial, and appendiceal cancers as well as one patient with melanoma.

The phase 2 CodeBreak 100 (NCT03600883)[24] trial studied sotorasib in patients with metastatic *KRAS*^{G12C}-mutant CRC who had progressed on prior fluoropyrimidine, oxaliplatin, and irinotecan treatment, using the phase 1 dosing of 960mg daily.[25] The ORR was 9.7% and the DCR was 82.3%. The median PFS in this group was 4 months, similar to the phase 1 trial. The adverse events profile was also similar with 7 (12%) patients experiencing a grade 3 or 4 event. A phase 2 trial also studied sotorasib in patients with *KRAS*^{G12C}-mutant advanced NSCLC who had progressed on prior platinum-based chemotherapy and programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) therapy. A total of 124 patients were evaluated for response, which resulted in an ORR of 37.1% with 4 (3.2%) patients who achieved a complete response. The DCR was 80.6%, the median PFS was 6.8 months, and the OS was 12.5 months.[26]

Adagrasib (MRTX849)

The KRYSTAL-1 study (NCT03785249)[27] is a phase 1/2 study investigating adagrasib in patients with advanced or metastatic solid tumors harboring a *KRAS*^{G12C} mutation. Patients were all previously treated with chemotherapy, anti-PD -1/PD-L1 therapy, or both. The phase 1/1b dose expansion phase established a dose of 600mg twice daily. Of the 25 patients enrolled, 2 patients had CRC who received the phase 2 dose and were evaluable. One patient achieved a partial response with a duration of response of 4.2 months. Of the 15 patients with NSCLC, the median PFS was 11.1 months and median OS was not reached. The ORR was 53.3%. A total of 36% of patients experienced a grade 3–4 treatment-related adverse event with fatigue being the most common (15%) at the phase 2 dose.[28] The phase 2 portion of this trial is ongoing. Interim analysis in August 2020 reported the data on 79 patients with pretreated NSCLC who received adagrasib at 600mg twice daily. Among the 51 evaluable patients (including those from the phase 1/1b cohort), the ORR was 45%. The DCR was 96%.[23] Updated analysis of monotherapy in CRC patients in May 2021 included 45 evaluable patients with an ORR of 22% and a DCR of 87%. Median PFS was 5.6 months.[29]

Differences Between Sotorasib and Adagrasib

In addition to the maturing clinical data on sotorasib and adagrasib, there are several differences between the two agents. Both drugs share a chemical backbone and target the same S-IIP region of KRAS, but differences in chemical structure led to a mean half-maximum inhibitory concentration (IC_{50}) of 47.9 nM for sotorasib and 89.9 nM for adagrasib. The half-life of adagrasib at 24.7 hours is also considerably longer than sotorasib, which is reported to be 5.5 hours.[30,31] In mouse models, sotorasib had an oral bioavailability of 22–40% compared to 62.9% with adagrasib.[32] Pre-clinical models

also demonstrate different affinities for on-target resistance mutations between the two agents, as discussed below.[33] While the clinical implications of these differences are not yet clear in human trials, there will likely be distinct characteristics of each drug with unique applications in select patient populations.

Mechanisms of Resistance to KRAS^{G12C} Inhibitors

Despite the early clinical data suggesting activity of the KRAS^{G12C} inhibitors in various cancer types, responses appear to be limited when used as monotherapy. There are several key mechanisms of resistance that have been identified in pathways both upstream and downstream of KRAS (Figure 1).[34] In pre-clinical models of resistant *KRAS*^{G12C}-mutant cancer, secondary *KRAS* mutations were the most common. Specific mutations such as G13D, R68M, and A59S/T appeared to confer resistance to sotorasib while remaining sensitive to adagrasib. The Q99L alteration was resistant to adagrasib but sensitive to sotorasib.[33] However, the most common mutation was Y96D/S, and this mutation conferred the strongest resistance against both sotorasib and adagrasib.[33] Low allele frequency hotspot mutations in *KRAS, NRAS, MRAS*, and *BRAF* were also able to confer resistance. Single-cell sequencing identified that many cells with these secondary mutations still harbor *KRAS*^{G12C}, suggesting that ongoing inhibitor activity does not need to be disrupted to manifest resistance.[35] An additional escape mechanism is the production of new KRAS^{G12C} protein in the GTP-bound state, which does not interact with existing inhibitors, thus avoiding inactivation.[36]

Further investigation of the patients who progressed on the KRYSTAL-1 study revealed that 17 (45%) had a potential underlying cause of resistance as identified by next-generation sequencing of tissue or circulating tumor DNA (ctDNA). Nine of these patients had secondary mutations of the *KRAS* gene or amplification of the *KRAS*^{G12C} allele. Twelve had molecular alterations in non-*KRAS* genes that were key components of other parts of the RAS/MAPK signaling pathways such as activating mutations of *BRAF, MAP2K1, NRAS*, and *RET*. Gene fusions of *RET, RAF1, BRAF, ALK*, and *FGFR3* were also observed. These mechanisms of resistance were not mutually exclusive as 7 patients had multiple concurrent mechanisms. Two NSCLC patients transformed to squamous cell histology.[37] Similarly, post-treatment specimens from 43 patients in the CodeBreak 100 and CodeBreak 101 (NCT04185883)[38] trials with sotorasib revealed new alterations in *KRAS, NRAS, BRAF, EGFR, FGFR2, Myc*, and others, in 27 patients. Six patients had undetectable *KRAS*^{G12C} alleles by ctDNA assessment.[35]

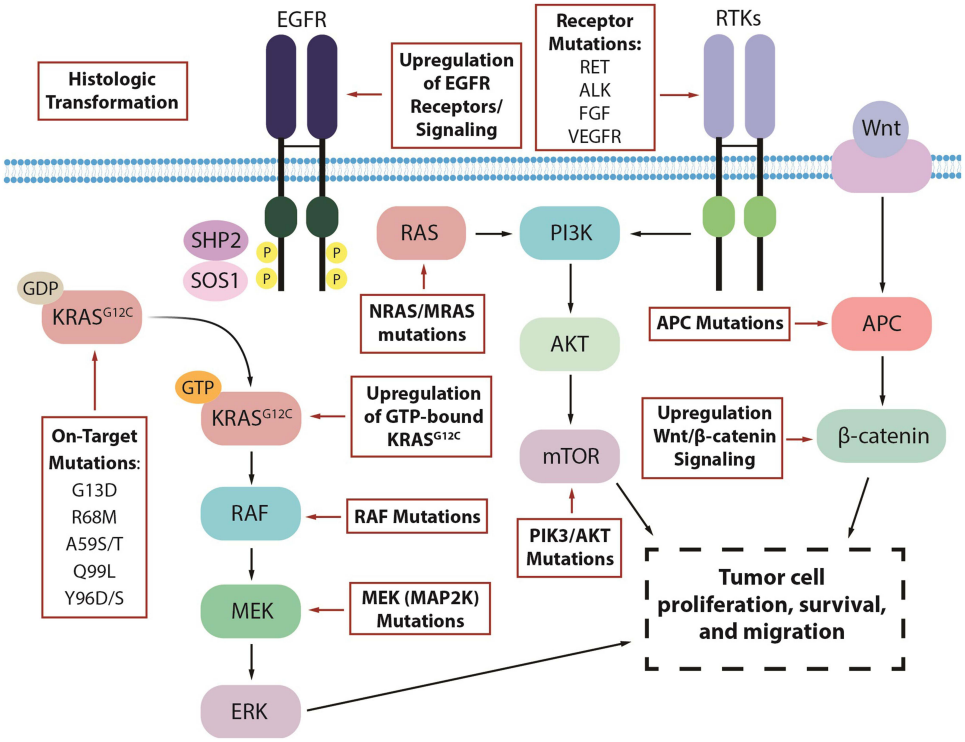

Figure 1 Proposed mechanisms of resistance to KRAS^{G12C} inhibitors in *KRAS*^{G12C}-mutated colorectal cancer.

Histologic evaluation in a rapid-autopsy case in a patient with KRAS^{G12C} inhibitor resistant NSCLC also observed non-cell autonomous mechanisms of resistance including remodeling of the tumor microenvironment.[39]

KRAS^{G12C} Inhibitors are Less Effective in CRC Compared to NSCLC Due to Key Mechanisms of Resistance

Among the sotorasib outcomes to date, the efficacy of single agent KRAS^{G12C} inhibition in CRC has been much lower when compared to the efficacy seen in NSCLC (Table 1). This diminished response is in line with the experience using other MAPK pathway inhibitors. For example, BRAF inhibition in *BRAF*^{V600E}-mutant colorectal cancer, with or without a MEK inhibitor, appears to be considerably less effective than what is seen in melanoma or NSCLC carrying the same alteration.[40–42] This resistance is likely due to key differences in the biology and mechanism of oncogenesis of CRC tumors. For example, in *BRAF*^{V600E}-mutant disease, acquired or pre-existing co-mutations in *PIK3* and *PTEN* were more prevalent in CRC samples.[43] In *KRAS*-mutant CRC, preclinical data suggests that oncogenesis is more heavily dependent on the KRAS signaling pathway, making primary resistance to KRAS inhibition less likely. Instead, rapid development of treatment-induced resistance appears to be the predominant issue.[44] In contrast, *KRAS*-mutant NSCLC may have more primary resistance as there is a clear subgroup of disease which is less dependent on KRAS signaling alone despite harboring *KRAS* mutations.[45] However, tumors that are sensitive appear to have a less rapid accumulation of resistance to KRAS inhibition compared to CRC.

While many of the mechanisms of resistance are shared among *KRAS*^{G12C}-mutant CRC and NSCLC, there are characteristic differences that may be drivers of the limited response to treatment in CRC. Amodio et al demonstrated that in *KRAS*^{G12C}-mutant CRC cell lines there is a much higher basal receptor tyrosine kinase (RTK) activation compared to NSCLC cell lines. This was also seen in clinical tissue samples where CRC tumors had more detectable phosphorylated RTKs. In particular, EGFR receptors appeared to be the primary activated subgroup. When treated with sotorasib, CRC cells showed initial response with concurrent down-regulation of ERK phosphorylation, but this was followed with a quick rebound in phosphorylated ERK levels within 24 hours of treatment. This rapid resistance was not seen in the NSCLC cell lines which showed further down-regulation of ERK phosphorylation over time. The CRC cells were also persistently sensitive to growth factor despite KRAS inhibition.[46] This increased RTK signaling is coupled with other mechanisms of resistance such as increased GTP-bound KRAS^{G12C} protein to maintain active downstream signaling and thus leads to tumor progression.[36] Alternative activated pathways more prevalent in CRC such as the Wnt/β-catenin pathway also interact with mutant KRAS signaling and degradation, promoting persistent oncogenic signaling and conferring resistance.[47]

Table 1 Summary of Trials of KRAS^{G12C} Inhibitors in Chemotherapy-Resistant CRC vs Immunotherapy and Chemotherapy Resistant NSCLC

	Colorectal Cancer			Non-Small Cell Lung Cancer		
	ORR (%)	DCR (%)	PFS (Mos)	ORR (%)	DCR (%)	PFS (Mos)
Sotorasib						
Hong et al[22]	7.1	73.8	4	32.2	88.1	6.3
Fakih et al[25]	9.7	82.3	4	–	–	–
Skoulidis et al[26]	–	–	–	37.1	80.6	6.8
Adagrasib						
Ou et al[28]	–	–	–	53.3	–	11.1
Jänne et al[23]	–	–	–	45.0	96.0	–
Weiss et al[29]	22	87	5.6	–	–	–

Combination with Anti-EGFR Therapy to Improve Response of KRAS^{G12C} Inhibitors in CRC

In order to potentiate the effect of KRAS^{G12C} inhibitors and suppress early mechanisms of resistance, a combination approach of sotorasib or adagrasib with EGFR inhibitors such as panitumumab or cetuximab is an approach that is currently being tested. Preclinical work demonstrates that cetuximab sensitizes *KRAS*^{G12C}-mutated CRC cell lines to sotorasib and leads to sustained down-regulation of phosphorylated *MEK* and *ERK* proteins, which ultimately causes arrest of cell proliferation and cell death. This has been subsequently tested in patient-derived organoids and xenograft models, both showing resistance with single-agent therapy (either KRAS^{G12C} or anti-EGFR inhibition alone) versus significant synergistic effect when used in combination.[46] The success of a combinatorial approach has been particularly well demonstrated with *BRAF*^{V600E}-mutant colorectal cancer where single-agent BRAF inhibition alone only led to a 5% response rate.[48] Combination therapy with EGFR inhibition in the BEACON trial showed a significant improvement in ORR to 26% as well as superior PFS and OS.[49,50] Comparable response rates were also seen when using cetuximab, vemurafenib, and irinotecan in combination.[51,52] This has led to the approval of the combination of encorafenib and cetuximab in pre-treated patients with *BRAF*^{V600E}-mutated metastatic colorectal cancer.

Trials are already ongoing with sotorasib and adagrasib combined with panitumumab and cetuximab, respectively. CodeBreak 101 is an umbrella phase 1b trial studying sotorasib in combination with various agents, including panitumumab. As of April 2021, 26 patients have been treated with this combination with a promising ORR (confirmed and unconfirmed) of 33%.[53,54] So far, no unexpected adverse events outside of those known for sotorasib and panitumumab have been seen. Similarly, the KRYSTAL-1 umbrella trial also had a cohort of patients who received adagrasib in combination with cetuximab and 32 patients have been enrolled as of July 2021. Among the 28 evaluable patients, the confirmed and unconfirmed ORR was 43% with a DCR of 100%. Again, the adverse events have been limited to those expected from the individual agents, with only 16% experiencing grade 3–4 toxicity.[29] These preliminary results are promising and further data from these trials are eagerly awaited as more patients are enrolled. Larger, confirmatory randomized trials in the second- and third-line settings are being conducted to further define the role of these combinations in metastatic colorectal cancer.

Emerging Strategies to Overcome Resistance to KRAS^{G12C} Inhibitors in CRC

While trials with the combination of KRAS^{G12C} inhibitors and EGFR inhibitors are ongoing, the advent of a new targeted therapy for CRC opens many new avenues of investigation and inquiry regarding the efficacy of these inhibitors in combination with existing therapies as well as new agents in the drug development pipeline (Figure 2). Additional cohorts in the CodeBreak 101 umbrella trial combine sotorasib with other approved agents including a MEK inhibitor, PD1/PD-L1 inhibitors, a CDK 4/6 inhibitor, an mTOR inhibitor, a VEGF inhibitor with various chemotherapies, as well as with other investigational agents. The KRYSTAL-1 umbrella trial is also exploring similar strategies.

The rationale is to potentiate the effect and preemptively target mechanisms of resistance. Several pre-clinical studies have provided strong rationales to move these combinations to the clinical setting. For example, the combination with trametinib, a MEK inhibitor, would inhibit the MAPK pathway and avoid early resistance through a bypass tract, thus deepening the response.[33] Early data from a phase 1 trial of sotorasib plus trametinib, including 18 patients with CRC, has demonstrated safety and some signals of efficacy with a median treatment duration of 84 days and no new or unexpected toxicity.[55]

Similarly, combination with CDK4/6 inhibitors such as palbociclib would block cell cycle entry despite activation of down-stream signaling pathways.[56] In vivo, when KRAS^{G12C} inhibitors were used alone, cell cycle progression was only modestly inhibited. Similarly, CDK4/6 inhibitors were unable to suppress RAS pathway signaling. However, adding Palbociclib to KRAS^{G12C} inhibitors demonstrated significantly more down-regulation of RAS pathway phosphorylation, cell division genes, and cell cycle progression.[57] Another strategy of adding everolimus, an mTOR inhibitor, has been shown to prevent resistance through the PI3K/mTOR pathway. In KRAS-mutant NSCLC mouse models, everolimus in combination with KRAS^{G12C} inhibitors was better at reducing cell viability when compared to either agent alone. The

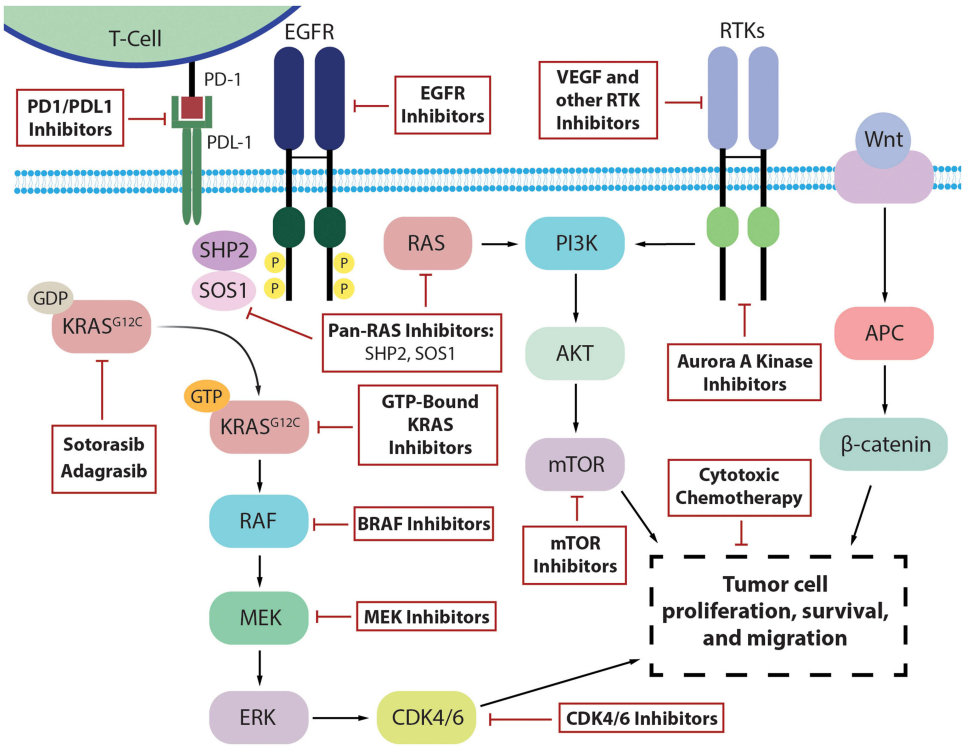

Figure 2 Existing and novel targets to potentially bypass resistance to $KRAS^{G12C}$ inhibition in $KRAS^{G12C}$-mutated colorectal cancer.

effect was further compounded by the addition of linsitinib, an IFG1 receptor inhibitor upstream of PI3K/mTOR, leading to complete suppression of cell proliferation.[58]

Beyond intracellular signaling mechanisms, synergistic combinations of $KRAS^{G12C}$ inhibitors with PD1/PDL-1 agents such as pembrolizumab and atezolizumab could lead to enhanced immune-related anti-tumor activity. Preclinical data with sotorasib showed increased CD8+ T cell infiltration, macrophages, and dendritic cells in the tumor microenvironment. PD-1 expression on the associated CD8+ T cells was also moderately increased. When sotorasib was used in combination with immune-checkpoint inhibitors, there was a significant increase in the number of mice with complete regression (nine of ten) compared to the agents used as monotherapy (one of ten).[17] Furthermore, combinations with chemotherapy such as FOLFIRI or FOLFOX as well as VEGF inhibitors such as bevacizumab can optimize anti-tumor inflammation and immunity and thus further increase efficacy.

Additionally, there are many investigational agents with strong pre-clinical data now moving into the clinical setting in combination with $KRAS^{G12C}$ inhibition. For instance, the strategy of simultaneously targeting other components of the KRAS scaffold shows promise. One target is SHP2, a tyrosine phosphatase that has been shown to promote KRAS signaling and progression in CRC when activated.[59] Inhibition of SHP2 increases GDP-bound $KRAS^{G12C}$ and there is in vitro evidence of synergism with $KRAS^{G12C}$ inhibitors.[60] Novel SHP2 inhibitors such as TNO155, BBP-398, and RMC-4630 are in ongoing phase 1 trials with concurrent plans to test in combination with $KRAS^{G12C}$ inhibition.[61–63] SOS1 is another component of the scaffold integral to KRAS function, and BI-3406 is an SOS1 inhibitor that has demonstrated activity in resistant $KRAS^{Y96D/S}$ cells in combination with trametinib.[33] Another agent is VIC-1911, an Aurora A Kinase (AURKA) inhibitor, which has pre-clinical data showing efficacy in resistant $KRAS^{G12C}$-mutant NSCLC cells when used in combination with WEE1 inhibition.[64] Finally, targeting $KRAS^{G12C}$ in its GTP-bound state with inhibitors such as RM-032 would bypass mechanisms of resistance such as overexpression of active GTP-bound $KRAS^{G12C}$ protein, which are not targetable with the current agents.[65]

Future Directions

Beyond early phase trials with the aforementioned combinations, randomized Phase 3 trials will be necessary to establish the efficacy of both sotorasib and adagrasib and move them forward as standard of care. Efforts are already underway. For instance, KRYSTAL-10 (NCT04793958)[66] is an open-label, randomized phase 3 trial comparing adagrasib plus cetuximab versus chemotherapy in the second-line setting for patients with *KRAS*^{G12C} metastatic CRC. NCT05198934[67] is a phase 3 multicenter, randomized trial of sotorasib and panitumumab versus investigator's choice (trifluridine and tipiracil or regorafenib) in previously treated metastatic *KRAS*^{G12C}-mutant CRC. In NSCLC, CodeBreak200 (NCT04303780)[68] is a randomized phase 3 trial comparing sotorasib with docetaxel in previously treated patients with locally advance or metastatic disease. Other planned trials will study sotorasib as first-line therapy for those with *KRAS*^{G12C}-mutant metastatic disease (NCT04933695)[69] as well as using sotorasib in conjunction with chemotherapy in the neoadjuvant setting for stage IIA-IIIB *KRAS*^{G12C}-mutant NSCLC (NCT05118854).[70]

Beyond KRAS^{G12C} inhibition, there still remains limited options for patients harboring other *KRAS* mutations found in the remaining 97% of *KRAS*-mutant CRC. However, there are agents on the horizon targeting mutational subtypes G12F, G12V, and G12R with RMC-6236 and G12D with MRTX1133.[71,72] Furthermore, targeting SOS1 and disrupting the KRAS scaffold may not be limited to KRAS^{G12C} and agents such as BI-1701963 are being tested as monotherapy in patients with any *KRAS* mutant cancer.[73]

Conclusion

After years of drug development, there are now finally targeted agents for a subgroup of *KRAS*-mutant cancers. Early phase 1/2 data has shown sotorasib and adagrasib to be safe and efficacious in the clinical setting. While *KRAS*^{G12C}-mutant NSCLC appears to have the best and most durable response to therapy, patients with *KRAS*^{G12C}-mutant CRC are also seeing some benefit. For those who have been through several lines of therapy, the benefit of a well-tolerated targeted agent can be meaningful even if the duration of response is limited. Yet the development of KRAS^{G12C} inhibitors in CRC has only just begun and there is a need for more data using combination therapy, larger randomized trials, and ultimately novel inhibitors for other, more prevalent, *KRAS* mutations.

Disclosure

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